Association between Body Mass Index and Risk of Gastric Cancer by Anatomic and Histologic Subtypes in Over 500,000 East and Southeast Asian Cohort Participants

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ABSTRACT

Background: This study was performed to investigate the association between body mass index (BMI) and gastric cancer in East and Southeast Asia where most of gastric cancer is non-cardia gastric cancer.

Methods: On the basis of 8,997 gastric cancer cases among the Asia Cohort Consortium participants from China, Japan, Korea, and Singapore ($N = 538{,}835$), we assessed gastric cancer risk according to BMI by calculating hazard ratios (HR) and 95% confidence intervals (CI) using the Cox proportional hazard regression model.

Results: A U-shaped associations between BMI and gastric cancer risk were observed. Gastric cancer risks in underweight group (<18.5 kg/m^2) and in obesity group (≥27.5 kg/m^2) were higher than reference BMI group (23–24.9 kg/m^2; HR, 1.15; 95% CI, 1.05–1.25 for underweight; HR, 1.12; 95% CI, 1.03–1.22 for obesity, respectively). The associations of underweight and obesity with gastric cancer risk were consistent in the analyses for non-cardia gastric cancer, intestinal-type gastric cancer, and late-onset gastric cancer. No significant association of underweight and obesity with the risk of cardia gastric cancer, diffuse-type gastric cancer, and early-onset gastric cancer was observed. In addition, we found that the U-shaped association between BMI and gastric cancer risk remained in nonsmokers, while only underweight was related to increased gastric cancer risk in smokers.

Conclusions: BMI has a U-shaped association with gastric cancer risk in East and Southeast Asian population, especially for the non-cardia gastric cancer, intestinal-type gastric cancer, and late-onset gastric cancer.

Impact: Future studies with consideration of anatomic location and histology of gastric cancer are needed to establish the association of underweight as well as obesity with gastric cancer risk.

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Introduction

Gastric cancer is the fifth most frequently diagnosed cancer worldwide, with the estimated new cases in excess of 1,000,000 in 2018 (1). Its incidence rate is the highest in East Asia, including China, Japan, and Korea (age-standardized incidence rate of 32.1 and 13.2 per 100,000 for men and women, respectively in 2018; ref. 1). Major risk factors for gastric cancer, such as *Helicobacter pylori* (*H. pylori*) infection and cigarette smoking account for over 85% of all gastric cancer cases (2). Furthermore, sodium intake over the recommendation of the World Health Organization (WHO) is attributable to more than 10% of gastric cancer incidence (3). However, there remains gastric cancer incidence that could not be explained by known risk factors above.

Excess body fatness has been defined as a risk factor for various cancers, such as esophagus (adenocarcinoma), liver, pancreas, kidney, endometrium, and breast (postmenopausal women; ref. 4). However, there were inconsistencies across results on assessing body fatness as a risk factor of gastric cancer. A previous meta-analysis on the association between gastric cancer and body fatness reported a sequential increase in gastric cancer risk from normal body mass index (BMI) to overweight and obesity (5–6). In contrast, another meta-analysis study found that there is no significant association of overweight or obesity with gastric cancer (7). A recent large retrospective cohort analysis using the Clinical Practice Research Datalink (CPRD) in United Kingdom reported an hazard ratio (HR) of 1.00 based on a linear model to evaluate gastric cancer risk with BMI which indicates no difference in gastric cancer risk according to BMI level, yielding a result supporting the latter meta-analysis (8–9). Those findings above raise the fundamental question of whether there is a significant association between BMI and gastric cancer risk, and the gastric cancer risk is linearly related to BMI or not if gastric cancer risk is related to BMI. In a nonlinear model using the same CPRD, in fact, an inverse J-shaped association of BMI with the gastric cancer risk was suggested. Elevated risks of gastric cancer were observed in underweight and BMI of 30 to 35 kg/m^2 (HR, 1.42 and 1.18, respectively; ref. 8) in this study.

The inconsistency on the association between gastric cancer risk and BMI may be because gastric cancer is not a single disease but consists of several sub-diseases with different clinical courses and causes, such as cardia and non-cardia gastric cancer according to anatomic location, diffuse and intestinal subtypes according to histologic findings (10).

The existing meta-analyses for only cardia gastric cancer showed consistent patterns in that the gastric cancer risk gradually increased from normal BMI to overweight and obesity (5–7). However, most of the results based on cardia gastric cancer were derived from North America and Europe (5–7, 11).

Because cardia gastric cancer is less than 10% among total gastric cancer in Asians (12) and the prevalence of obesity, BMI more than equal to 30 kg/m^2 according to WHO standards, is low compared with Western population (13–14), it is not easy to have sufficient statistical power to assess the association between obesity and cardia gastric cancer based on a single study in Asia. To overcome such limitations and to investigate the causal association between BMI and gastric cancer, a large-scale Asian prospective cohort study data is needed.

Therefore, we aimed to confirm a nonlinear association between BMI and the risk of overall gastric cancer and to identify the association between BMI and the risk of gastric cancer subtypes by anatomic and histologic classification in a large-scale prospective cohort study pooling project based on East and Southeast Asian population.

Materials and Methods

Study design and population

This study was based on the Asia Cohort Consortium (ACC), an international collaboration involving more than a million participants across Asia to investigate the etiology of various diseases. Details of ACC have been introduced in previous studies (15, 16). Thirteen cohorts from China, Japan, Korea, and Singapore recruiting 577,605 participants were included in this study. Relevant cohort investigators provided data on age, sex, country, year of recruitment, smoking status, alcohol drinking status, height, and weight at baseline along with gastric cancer incidence.

All covariates used in this study were harmonized by the ACC coordinating center. A dictionary containing details about data processing such as the contents of each variable, variable type, variable name, and precautions when handling variables is provided to each cohort. Each cohort send the data processed by the processing method written in the dictionary to the ACC coordinating center. Then, the ACC coordinating center confirm the content, format, and distribution of variables in the received data and integrates them into a unified format.

Height and weight were measured at baseline in all of the cohorts included in this study and participants without baseline height or weight data were excluded. We defined acceptable BMI range as 10.0 to 50.0 kg/m^2 and included participants within this range. We additionally excluded those lacking data on age at enrollment, gastric cancer incidence, or follow-up period, and total 554,037 subjects were left in this study. Because BMI in individual on the cusp of gastric cancer development, or in terminal illness, is usually low, there might be reverse causation between low BMI and gastric cancer. Hence, we excluded gastric cancer incidence diagnosed within 2 years from cohort enrollment and finally 538,835 study subjects including 8,997 gastric cancer cases were defined as study population. This study was approved by the institutional review board of Seoul National University Hospital (IRB No. H-0110–084–002 and H-0901–040–269) and followed the Declaration of Helsinki principles. All participants signed a written informed consent document.

Exposure and outcome

We used two classification criteria for BMI to find the association with gastric cancer risk in Asians. The first criterion is the BMI standard classification proposed by the WHO as follows: <18.5, 18.5–22.9, 23.0–24.9, 25.0–29.9, and ≥30.0 kg/m^2. However, there are a few obese Asians with BMI more than equal to 30.0 kg/m^2 (only 2.2% of the ACC participants) and there had been researches suggesting that the association between BMI, body fat, and health risk in Asians is different from that of Europeans. So we used the 2002′ modified BMI criterion for Asians suggested by WHO which can be applied to all ethnics in Asia (17), with criteria <18.5, 18.5–23, 23–25, 25–27.5, and ≥27.5 kg/m^2. The criteria had been used in previous ACC studies for association with mortality risk (16).

We defined gastric cancer incidence according to the International Classification of Diseases for Oncology 2nd/3rd version (C16.0-C16.9 for ICD-O-3 version; 151.0–151.9 for ICD-O-2 version). Follow-up period for gastric cancer incidence was defined as the interval between date of cohort enrollment and gastric cancer diagnosis date for cases or last follow-up date for non-cases. Of thirteen cohorts, eight cohorts included information on the specific gastric cancer location and pathologic type. Cardia gastric cancer and non-cardia gastric cancer were classified according to the ICD-O codes (for non-cardia gastric cancer, C16.1-C16.9 for ICD-O-3 version; 151.1–151.9 for ICD-O-2 version; for cardia gastric cancer, C16.0 for ICD-O-3 version; 151.0 for ICD-O-2 version).

Lauren's classification is one of the commonly used histologic classifications of gastric cancer and divides gastric cancer into mainly intestinal-type and diffuse-type according to tumor cells formation and behavior. Because two histologic types of gastric cancer (intestinal-type and diffuse-type) differ in pathology, epidemiology, and etiology, we chose this histologic classification in the analyses to assess the association between BMI and gastric cancer risk. Therefore, two major histologic types of gastric cancer—intestinal-type and diffuse-type gastric cancer—were considered in this study, and indeterminate-type or mixed carcinoma were excluded from the subgroup analysis.

Statistical analysis

To evaluate risk for gastric cancer incidence associated with BMI, we calculated HR and corresponding 95% confidence intervals (CI), in the Cox proportional hazard regression models adjusted for potential confounders, including age at enrollment, sex, country (China, Japan, Korea, and Singapore), cohort, smoking status (never, past, and current), and alcohol drinking status (never and ever). All analyses were performed after excluding gastric cancer incidence diagnosed within 2 years from cohort enrollment. In addition, we performed the sensitivity analysis by excluding gastric cancer case diagnosed within 4-year follow-up period from cohort enrollment to evaluate the association between BMI and gastric cancer risk while minimizing the possibility of reverse causation. We confirmed the Cox proportional hazard assumption based on the log–log survival curve for each category of BMI and confirmed that the assumption was not violated by with parallel curves. We performed meta-analysis using both fixed-effects model and random-effects model and evaluated heterogeneity among studies using the I^2 and the Cochran Q statistics. We additionally performed the restricted cubic spline analysis by using the SAS LGTPHCURV9 macro code to assess nonlinear association between BMI and gastric cancer risk.

On eight cohorts included information on the specific gastric cancer location and pathologic type, we performed subgroup analysis according to anatomic location (non-cardia gastric cancer vs. cardia gastric cancer), pathologic-type (intestinal-type gastric cancer vs. diffuse-type gastric cancer), and age onset in gastric cancer cases [late-onset (onset age > 70-year), mid-aged onset (45-year < onset age ≤70-year), and early-onset (onset age ≤45-year)]. We included unspecified gastric cancer (C16.9 for ICD-O-3 version; 151.9 for ICD-O-2 version; $N = 2{,}014$) and gastric cancer without information on ICD-O code ($N = 2{,}182$) within the non-cardia gastric cancer group because most of gastric cancer cases identified in Asian countries are non-cardia gastric cancer, especially Japan and Korea reporting a proportion of non-cardia gastric cancer higher than 90% (12).

To assess the impact of smoking status on the association between BMI and gastric cancer risk, we classified study subjects into groups according to a cigarette smoking status, and evaluated gastric cancer risk according to BMI levels in each stratified group. We additionally assessed the association between BMI and gastric cancer risk in each stratified population by sex.

All statistical analyses were performed using the SAS, version 9.4 (SAS Institute, Cary, NC).

Data Availability

The data underlying this article were provided by ACC by permission. Data will be shared on request with the permission of the corresponding author and ACC.

Results

Participants in their respective cohorts were enrolled during 1984–2006 and followed for a median period of 14.9 years. Among 554,037 participants in the study, a total of 10,006 gastric cancer cases were recorded during the follow-up period (**Table 1**) and 8,997 gastric cancer cases were left after excluding those diagnosed within 2 years from the cohort enrollment. Overall, men, cigarette smokers, and alcohol drinkers comprised 45.3%, 39.8%, and 40.5% of the subjects, respectively (data partially shown in **Table 1**). Mean age at enrollment was 54.4 years, with variation across the cohorts. Mean BMI at baseline was 23.3 kg/m^2 (SD, 3.2 kg/m^2). Most of gastric cancer cases were non-cardia gastric cancer (including unspecified gastric cancer; 93.2%) in this study subjects. Intestinal-type gastric cancer was more prevalent than diffuse-type gastric cancer in this study (73.0% vs. 6.4%).

No significantly increased gastric cancer risk was observed in the obese group defined as BMI ≥30 kg/m^2 according to BMI classification by previous WHO standards (HR, 1.08; 95% CI, 0.93–1.25; Supplementary Table S1). However, significantly increased gastric cancer risks were found in the underweight group (BMI < 18.5 kg/m^2) and obese group defined as the new WHO standard for Asians (BMI ≥ 27.5 kg/m^2; HR, 1.15; 95% CI, 1.05–1.25 for underweight; HR, 1.12; 95% CI, 1.03–1.22 for obesity, respectively), compared with the reference BMI (23.0–24.9 kg/m^2; **Table 2**). The results based on Asian BMI standards were persistent even in a limited group not exposed to tobacco smoking (HR, 1.23; 95% CI, 1.06–1.43 for underweight; HR, 1.23; 95% CI, 1.08–1.39 for obesity, respectively). The U-shaped association between BMI and gastric cancer risk was reconfirmed in the results from the restricted cubic spline model (Supplementary Fig. S1).

Moreover, the association between BMI level and gastric cancer risk was also consistent in the meta-analysis based on the fixed-effect model (HR, 1.12; 95% CI, 1.03–1.22 for underweight; HR, 1.21; 95% CI, 1.01–1.48 for obesity, respectively). Although there was a significant heterogeneity between cohorts in the association between BMI and gastric cancer risk, no individual study alone led to the results of the pooled analysis (Supplementary Figures S2–S5). In subgroup analysis by ethnicity, the U-shaped associations of BMI with gastric cancer risk were found only in East Asians, not Southeast Asians (Supplementary Table S2). In sensitivity analysis excluding gastric cancer cases confirmed within 4 years from cohort enrollment, the U-shaped association between BMI and gastric cancer risk remained (Supplementary Table S3).

The U-shaped association with BMI also remained in non-cardia gastric cancer subtype, (HR, 1.22; 95% CI, 1.10–1.35 for underweight; HR, 1.09; 95% CI, 0.98–1.21 for obesity, respectively; **Table 3**). The similar pattern was also found in intestinal-type gastric cancer subtype (HR, 1.14; 95% CI, 1.01–1.28 for underweight; HR, 1.11; 95% CI, 0.98–1.25 for obesity, respectively). There were some differences in the pattern of association between intestinal-type gastric cancer subtype and BMI according to sex. The associations of increased intestinal-type gastric cancer risk with underweight was observed only in women (HR, 1.51; 95% CI, 1.24–1.83), and obesity was associated with elevated risk of intestinal-type gastric cancer only in men (HR, 1.13; 95% CI, 0.97–1.32), though this association was not statistically significant (**Table 4**). In contrast, no significant association with the risk of cardia gastric cancer and diffuse-type gastric cancer was observed in underweight and obesity groups (**Tables 3** and **4**). The U-shaped association was also found in late-onset gastric cancer (HR, 1.13; 95% CI, 1.01–1.26 for underweight; HR, 1.21; 95% CI, 1.08–1.36 for obesity, respectively); whereas early-onset gastric cancer risk was not associated with BMI levels (**Table 5**).

Table 1. Baseline characteristics of the participating cohorts in the ACC from 1984 to 2015.

	Person-year	Cohort	Enrollment Year	Follow-up year Median (IQR)	Men %	Age Mean (SD)	Gastric cancer Cases N	BMI[a] (kg/m²) <18.5 %	18.5–22.9 %	23–24.9 %	25–29.9 %	≥30.0 %
ACC	7,991,847	554,037	1984–2006	14.9 (10.5–17.6)	45.3	54.4 (10.3)	10,006	5.4	43.4	24.7	23.7	2.8
Japan												
RERF	1,106,385	49,730	1963–1993	22.5 (11.3–32.9)	39.7	52.2 (13.7)	2,355	13.3	53.9	17.1	13.8	1.9
3pref. Miyagi	340,460	29,457	1984	15.0 (7.8–15.0)	44.9	56.8 (11.1)	286	5.3	45.0	24.0	23.1	2.7
3pref. Aichi	371,202	32,178	1985	15.2 (7.5–15.3)	47.4	56.2 (11.3)	582	10.0	54.3	20.9	13.8	1.0
Miyagi	703,009	43,776	1990	17.6 (17.6–17.6)	48.2	51.9 (7.5)	799	2.4	41.4	26.7	26.8	2.7
Takayama	402,895	29,654	1992	15.6 (15.5–15.6)	45.7	55.4 (12.7)	628	8.6	54.6	21.8	14.2	0.9
JPHC1	890,403	42,641	1990–1992	22.6 (22.1–22.8)	47.8	49.6 (5.9)	1,016	2.6	42.2	26.5	26.0	2.7
JPHC2	978,828	55,571	1993–1995	19.7 (18.7–19.8)	47.4	54.2 (8.8)	1,359	3.6	43.2	25.4	25.0	2.8
Ohsaki	482,367	44,741	1995	13.2 (9.6–13.2)	48.1	59.8 (10.3)	899	3.7	41.4	25.8	26.3	2.9
Korea												
KMCC	260,383	18,961	1993–2004	13.4 (10.9–17.4)	40.0	53.7 (14.4)	403	4.5	40.9	23.5	27.7	3.5
KNCC	37,562	7,747	2002–2015	4.7 (3.4–6.2)	36.0	52.7 (8.4)	23	2.2	41.7	26.2	27.0	2.9
Singapore												
SCHS	723,842	63,240	1993–1999	12.4 (9.8–13.8)	44.2	56.5 (8.0)	641	6.5	41.6	29.8	19.2	3.0
China												
SMHS	579,937	61,436	2001–2006	9.6 (9.0–10.7)	100	55.4 (9.7)	562	4.3	36.6	26.1	30.5	2.6
SWHS	1,114,574	74,905	1996–2000	15.3 (14.7–16.0)	0.0	52.6 (9.1)	453	3.4	37.5	23.7	30.2	5.1

Abbreviations: IQR, Interquartile range; SD, Standard deviation; *N*, Number; RERF, Radiation Effects Research Foundation; 3pref. Miyagi, Three-Prefecture Cohort Study, Miyagi; 3pref. Aichi, Three-Prefecture Cohort Study, Aichi; JPHC1, Japan Public Health Center-based prospective Study1; JPHC2, Japan Public Health Center-based prospective Study2; KMCC, Korean Multi-center Cancer Cohort; KNCC, Korean National Cancer Screenee Cohort; SCHS, Singapore Chinese Health Study; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.
[a]Mean of BMI = 23.3 kg/m² (SD, 3.2 kg/m²).

The associations of underweight and obesity with increased risk of non-cardia gastric cancer, intestinal-type gastric cancer, and late-onset gastric cancer were persistent even when we excluded gastric cancer cases diagnosed within 4 years from cohort enrollment (Supplementary Tables S4–S6).

Among nonsmokers, a U-shaped association of BMI on gastric cancer risk was consistently observed (HR, 1.23; 95% CI, 1.06–1.43 for underweight; HR, 1.23; 95% CI, 1.08–1.39 for obesity, respectively; Supplementary Table S7). In contrast, the impact of underweight on increasing gastric cancer risk lessened and the elevation of gastric cancer risk in obesity group was not observed in smokers (HR, 1.12; 95% CI, 0.99–1.25 for underweight; HR, 1.00; 95% CI, 0.88–1.14 for obesity, respectively).

Discussion

We found elevated gastric cancer risk in both underweight and obesity groups based on this prospective cohort study consisting

Table 2. BMI and risk for gastric cancer in the ACC[a] from 1984 to 2015.

	BMI (kg/m²) < 18.5	18.5–22.9	23.0–24.9	25.0–27.4	≥ 27.5[c]
Cohort					
HR (95% CI)[b]	1.15 (1.05–1.25)	1.07 (1.02–1.13)	1	1.01 (0.94–1.08)	1.12 (1.03–1.22)
Person-year	419,544	3,519,088	1,947,967	1,355,198	734,302
Cases, *N*	692	4,290	1,977	1,318	720
Cohort with nonsmoking and nondrinking					
HR (95% CI)[b]	1.23 (1.06–1.43)	1.10 (1.01–1.20)	1	1.12 (1.00–1.24)	1.23 (1.08–1.39)
Person-year	236,973	2,052,568	1,172,545	836,105	488,037
Cases, *N*	234	1,492	761	599	386
Meta-analysis					
HR (95% CI)[d]	1.01 (0.85–1.20)	1.06 (0.98–1.14)	1	1.00 (0.92–1.09)	1.13 (1.02–1.25)
HR (95% CI)[e]	1.12 (1.03–1.22)	1.08 (0.95–1.23)	1	1.05 (0.86–1.27)	1.21 (1.01–1.48)
I^2 (%)	58%	51%		25%	23%
$P_{\text{Cochran Q test}}$	0.07	0.08		0.46	0.49

[a]Analyzed excluding cases diagnosed within 2 years of cohort enrollment.
[b]Adjusted for age at cohort enrollment, sex, country, ever cigarette smoking status and ever alcohol drinking status.
[c]Participants with BMI ≥ 27.5 kg/m² are 9.2% and 8.9% among ACC cohort population and incident gastric cancer cases, respectively.
[d]Random effects model.
[e]Fixed effect model.

Table 3. BMI and risk for gastric cancer subtype according to anatomic location in the ACC[a].

	BMI (kg/m²)				
	<18.5	18.5–22.9	23.0–24.9	25.0–27.4	≥27.5
CGC					
HR (95% CI)[b]	0.89 (0.58–1.38)	0.99 (0.78–1.26)	1	1.16 (0.86–1.57)	0.94 (0.62–1.43)
Cases, *N*	27	227	100	76	28
NCGC[c]					
HR (95% CI)[b]	1.22 (1.10–1.35)	1.09 (1.02–1.16)	1	0.97 (0.89–1.05)	1.09 (0.98–1.21)
Cases, *N*	540	3,126	1,341	858	449
Female					
CGC					
HR (95% CI)[d]	1.46 (0.75–2.85)	0.72 (0.43–1.19)	1	0.92 (0.50–1.69)	0.46 (0.19–1.12)
Cases, *N*	15	41	25	19	8
NCGC[c]					
HR (95% CI)[d]	1.42 (1.20–1.68)	1.09 (0.97–1.22)	1	1.00 (0.86–1.16)	1.05 (0.89–1.24)
Cases, *N*	224	992	427	314	197
Male					
CGC					
HR (95% CI)[d]	0.68 (0.37–1.27)	1.17 (0.89–1.54)	1	1.20 (0.85–1.70)	1.06 (0.65–1.73)
Cases, *N*	12	186	75	57	20
NCGC[c]					
HR (95% CI)[d]	1.15 (1.01–1.31)	1.09 (1.01–1.18)	1	0.95 (0.86–1.06)	1.12 (0.97–1.29)
Cases, *N*	316	2,134	914	544	252

Abbreviations: CGC, Cardia gastric cancer; NCGC, Non-cardia gastric cancer.
[a]Analyzed excluding cases diagnosed within 2 years from cohort enrollment.
[b]Adjusted for age at cohort enrollment, sex, country, ever cigarette smoking status and ever alcohol drinking status.
[c]Cases including unspecified gastric cancer.
[d]Adjusted for age at cohort enrollment, country, ever cigarette smoking status and ever alcohol drinking status.

of more than 500,000 Asians. According to the anatomic subtype, non-cardia gastric cancer, which accounts for the majority of gastric cancer in Asians, was also related to the BMI in the same manner of association between BMI and overall gastric cancer risk. Intestinal-type and late-onset gastric cancers also exhibited patterns of association with BMI similar to those observed for total gastric cancer.

Several epidemiologic studies suggested a U-shaped pattern on the association between BMI and gastric cancer risk, but none of them

Table 4. BMI and risk for gastric cancer subtype according to histologic classification in the ACC[a].

	BMI (kg/m²)				
	<18.5	18.5–22.9	23.0–24.9	25.0–27.4	≥27.5
Intestinal-type gastric cancer					
HR (95% CI)[b]	1.14 (1.01–1.28)	1.07 (0.99–1.15)	1	0.96 (0.87–1.06)	1.11 (0.98–1.25)
Cases, *N*	400	2,455	1,065	664	360
Diffuse-type gastric cancer					
HR (95% CI)[b]	0.99 (0.63–1.55)	1.22 (0.95–1.57)	1	1.17 (0.85–1.61)	1.27 (0.85–1.89)
Cases, *N*	26	224	83	67	35
Female					
Intestinal-type gastric cancer					
HR (95% CI)[c]	1.51 (1.24–1.83)	1.10 (0.96–1.26)	1	1.00 (0.84–1.19)	1.07 (0.88–1.30)
Cases, *N*	167	718	304	226	148
Diffuse-type gastric cancer					
HR (95% CI)[c]	0.96 (0.53–1.74)	1.06 (0.75–1.49)	1	0.97 (0.62–1.52)	1.14 (0.69–1.89)
Cases, *N*	15	111	48	33	22
Male					
Intestinal-type gastric cancer					
HR (95% CI)[c]	1.02 (0.88–1.19)	1.06 (0.97–1.16)	1	0.94 (0.83–1.05)	1.13 (0.97–1.32)
Cases, *N*	233	1,737	761	438	212
Diffuse-type gastric cancer					
HR (95% CI)[c]	1.09 (0.55–2.18)	1.47 (1.00–2.15)	1	1.50 (0.93–2.41)	1.49 (0.79–2.83)
Cases, *N*	11	113	35	34	13

[a]Analyzed excluding cases diagnosed within 2-year from cohort enrollment.
[b]Adjusted for age at cohort enrollment, sex, country, ever cigarette smoking status and ever alcohol drinking status.
[c]Adjusted for age at cohort enrollment, country, ever cigarette smoking status and ever alcohol drinking status.

Table 5. BMI and risk for gastric cancer subtype according to onset age in the ACC[a].

	BMI (kg/m^2)				
	<18.5	18.5–22.9	23.0–24.9	25.0–27.4	≥27.5
Early-onset GC[b]					
HR (95% CI)[c]	1.07 (0.50–2.31)	1.19 (0.83–1.72)	1	1.08 (0.67–1.74)	0.84 (0.43–1.64)
Cases, N	8	97	41	29	11
Late-onset GC[b]					
HR (95% CI)[c]	1.13 (1.01–1.26)	1.03 (0.96–1.11)	1	1.03 (0.93–1.13)	1.21 (1.08–1.36)
Cases, N	523	2,467	1,046	683	391

[a]Analyzed excluding cases diagnosed within 2 years from cohort enrollment.
[b]The onset age of gastric cancer: 'Early onset' and 'Late onset' were defined as 'Onset age < 45-year' and 'Onset age > 70-year', respectively.
[c]Adjusted for age at cohort enrollment, sex, country, cohort, ever cigarette smoking status and ever alcohol drinking status.

could confirm the gastric cancer risk related to BMI level due to lack of statistical power (8, 18–20). One of the reasons was that it might be difficult to ascertain an increased risk of gastric cancer with underweight in the U.S. and European populations because underweighted people are rare and gastric cancer is uncommon compared with Asian population. On the contrary, in East Asians, obesity prevalence (BMI ≥ 30 kg/m^2) is only 1% to 5% (12), so it may be difficult to observe a high risk of gastric cancer in group with obesity.

In particular, cardia gastric cancer is known to be strongly associated with obesity; but the positive association was reported in only American and European studies (5, 11). There were three Asian population studies for cardia gastric cancer in relation to overweight or obesity. We conducted meta-analysis using previous three Asian studies (21–23), however increased risk of cardia gastric cancer in accordance with obesity was not confirmed (summary relative risk = 1.24; 95% CI, 0.93–1.66; Supplementary Fig. S6). In this study, we found that being overweight and obese in Asians did not increase the risk of cardia gastric cancer. Rather, excess BMI levels were associated with elevated risk for non-cardia gastric cancer, which was similarly observed in nested case–control studies derived from multiple Asian cohort studies (HpBCC; 20). Additional studies are warranted to investigate the underlying reasons for the observed difference in the BMI-cardia gastric cancer risk association between Asian and American/European populations.

In the cohort subjects who do not smoke with adjustment for alcohol drinking status, the risks of gastric cancer in underweight population and obese population were still higher than that in population with reference BMI, suggesting that BMI is an independent factor involving in gastric cancer development regardless of the confounding effects of smoking or alcohol drinking.

Our result for U-shaped association with BMI on the risk of gastric cancer could be interpreted under the following biological mechanism. In general population, underweight, one of the forms of malnutrition, is associated with micronutrient deficiency (24, 25) and consequently causes poor immunity (26, 27), and increase oxidative stress (28). These processes above can increase the gastric cancer risk by elevating the likelihood of *H. pylori* infection and diminishing prevention effect against cancer. In addition, smoking has been suggested to be inversely associated with body weight (29), thus smoking and low BMI are characteristics that can be clustered. When both factors exist concurrently, the carcinogenic effect of tobacco smoking may be greater due to a series of underweight courses for bad health mentioned above.

In contrast, the biological mechanism between overweight or obesity and gastric cancer risk may be the direct induction and progression of carcinogenesis due to a series of inflammatory responses and increased chronicity (30, 31). However, this was the mechanism explaining the association between the existing cardia gastric cancer and obesity. It has not been elucidated whether the association between non-cardia gastric cancer and obesity is due to chronic inflammatory condition. Therefore, additional studies are needed to determine mechanisms that could explain the link between non-cardia gastric cancer and overweight/obesity, especially in Asians.

In the analyses considering pathology and age at onset of gastric cancer, an elevation of gastric cancer risk according to underweight was observed only in case of intestinal-type gastric cancer and late-onset gastric cancer as well as non-cardia gastric cancer. It has been known that cardia gastric cancer is positively related to obesity and diffuse-type gastric cancer in North American and European studies, which is more commonly observed in young patients with gastric cancer and linked to hereditary factors rather than environmental factors compared with intestinal-type gastric cancer (32). In light of the link among cardia gastric cancer, diffuse-type, and young age onset in Westerners, it is a reasonable observation that the pattern of association of intestinal-type gastric cancer and late-onset gastric cancer with BMI in Asians having non-cardia gastric cancer in most cases (over 90%) is similar to the association between total gastric cancer and BMI.

When obesity was defined as the general obesity standard (BMI ≥ 30 kg/m^2) by the WHO, it could be interpreted that only underweight is linked to the increased risk of gastric cancer and obesity (BMI ≥ 30 kg/m^2) was not associated with an elevated gastric cancer risk in this current study. That result was clearly different from the previous meta-analyses showing a link between overweight/obesity and gastric cancer risk, mostly derived from Westerners' studies. Further research is needed to determine whether the difference is due to variation in race itself, or that in the composition of gastric cancer or the exposure to environmental factors.

This study has several limitations. First, we did not consider *H. pylori* infection as a confounder in the analysis, despite the fact that it might be the key link between BMI and gastric cancer risk. Second, as only eight cohorts from Japan and Korea of the consortium had information of anatomic location of gastric cancer, the associations of BMI with cardia gastric cancer and non-cardia gastric cancer risk are limited in generalization. Third, elevated gastric cancer risk related to underweight could arise from reversed causation. Therefore, we performed analyses after excluding gastric cancer cases identified within 2 years from enrollment to minimize the reverse causation.

Despite these limitations, this study has several strengths. There were over 8,997 gastric cancer cases in this study even after excluding gastric cancer cases confirmed within 2 years from cohort enrollment, meaning the sample had sufficient statistical power even after eliminating gastric cancer cases diagnosed within 2 years of enrollment.

This large-scale Asian cohort study presented results on whether the risk of gastric cancer according to BMI depends on the biological characteristics of gastric cancer (anatomic location, histologic type, and age onset), though information on characteristics of gastric cancer was available only in eight cohorts.

In conclusion, this large-scale Asian cohort study established that underweight and obesity based on the Asian obesity standard (BMI ≥ 27.5 kg/m^2) are associated with the increased risk of gastric cancer, especially non-cardia gastric cancer. The pattern in the association between BMI and gastric cancer risk was persistent in case of intestinal-type gastric cancer and late-onset gastric cancer. In contrast, even though this study was the largest Asian cohort study to date, increased risk of cardia gastric cancer in overweight and obese people in Asians could not be confirmed because the proportion of overweight and obese population is low and most of gastric cancer cases are non-cardia gastric cancer in Asians.

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Authors' Contributions

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Note

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